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THE PNEUMOCOCCIDAL POWER OF RABBIT SERUM AFTER THE ADMINISTRATION OF ETHYLHYDROCUPREIN HYDROCHLORID, QUININ AND UREA HYDROCHLORID, AND OTHER CINCHONA DERIVATIVES

STUDIES IN PNEUMONIA, VII

CHARLES WEISS

From the McManes Laboratory of Experimental Pathology of the University of Pennsylvania, Philadelphia

Previous studies by Solis-Cohen, Kolmer, Heist, and Steinfield on the mechanism of the action of cinchona derivatives in pneumonia of man have indicated the highly specific pneumococcidal action of these salts, both in vitro[1] and in vivo,[2] as well as an accelerating action on leukocytosis and phagocytosis in vitro.[3] In this article I wish to present briefly the results of studies of the pneumococcidal action of the serum of rabbits after the administration of ethylhydrocuprein hydrochlorid, quinin and urea hydrochlorid, and other cinchona compounds.

Wright[4] was first to observe the pneumococcidal action of the serum of human beings and mice treated with ethylhydrocuprein. He calls attention to the negative results obtained with rabbits. Scott[5] likewise obtained negative results with ethylhydrocuprein in the treatment of pneumococcus infections in rabbits. Boecker[6] thoroughly investigated this problem and also obtained negative results. Recently Moore and Chesney[7] in an extensive study on the use of ethylhydrocuprein in the treatment of acute lobar pneumonia in man pointed out the necessitw of repeated doses of the drug before any bactericidal action of the serum can be demonstrated. With this suggestion in mind and working with derivatives of cinchona less toxic than ethylhydrocuprein, it was hoped that increased pneumococcidal action of the serum of normal rabbits could be demonstrated.

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1 Jour. Infect. Dis., 1917, 20, 272.

2 Ibid., p. 313.

3 Ibid., p. 333.

4 On Pharmaco-therapy and Preventive Inoculation Applied to Pneumonia, 1915.

5 Jour. Path. and Bacteriol., 1914-1915, 19, p. 130.

6 Ztschr. f. Immunitätsforsch., O., 1915, 24, p. 148.

7 Arch. Int. Med., 1917, 19, p. 611.

Normal healthy rabbits weighing from 1,200-3,000 gm. were used. The drugs were ethylhydrocuprein hydrochlorid, quinin and urea hydrochlorid, quinin chlorhydrosulphate, and quinin dihydrobromid. For oral administration the proper dose of drug was dissolved in distilled water and given by means of the stomach tube. Physiologic saline solution was used as the menstruum for intravenous injections. Bleedings were made from the ear vein before administration of the drug and at intervals from half to two or more hours thereafter. All specimens were allowed to remain in the icebox over night to allow the serum to separate. The clear serum was used after sterilization by heating in a waterbath at 56 C. for one-half hour.

The organism employed was a virulent Type 1 pneumococcus from the Rockefeller Institute. Sixteen hour-old cultures in blood-glucose broth were used. The technic (Expers. 1 to 3) was that described by Moore and Chesney;[7] later we used the plating method of Kolmer.[8]

[8] Jour. Infect. Dis., 1917, 20, 293.

The protocols of a few typical experiments are given as illustrative of the results.

Exper. 1.—Single lethal dose of ethylhydrocuprein hydrochlorid by oral administrations. A rabbit weighing 2,200 gm. was given ethylhydrocuprein hydrochlorid by stomach tube in a dose of 0.4 gm. per kilo. The animal died 3½ hours after administration of the drug. No pneumococcidal action was demonstrated in the serum of the heart's blood taken immediately after death.

Exper. 2.—Single lethal intravenous dose of ethylhydrocuprein hydrochlorid. A rabbit weighing 1,500 gm. was given ethylhydrocuprein hydrochlorid intravenously in a dose of 0.02 gm. per kilo. The animal died immediately after injection with typical convulsion of cinchona poisoning. The serum obtained from the heart's blood showed no pneumococcidal action.

Exper. 3.—Single tolerated doses of quinin and urea hydrochlorid and quinin chlorohydrosulphate by oral administrations. Two rabbits weighing 1,000 and 1,700 gm. were given quinin and urea hydrochlorid, and quinin chlorohydrosulplate, respectively, by stomach tube in doses of 0.5 gm. per kilo of weight. The animals showed slight cinchonism but recovered. No pneumococcidal action was observed in serum obtained 5 hours after the injection.

Exper. 4.—Repeated doses of quinin and urea hydrochlorid, and quinin chlorohydrosulphate by oral administrations. Two rabbits weighing 1,500 and 3,000 gm. were given quinin and urea hydrochlorid by stomach tube in doses of 0.5 and 0.4 gm. per kilo, respectively. Three hours later each was bled and then given a second dose of 0.1 gm. per kilo by stomach tube. The second rabbit died immediately afterward and the heart blood was collected. The first rabbit was bled 2 hours later and again given a dose of the drug corresponding to 0.1 gm. per kilo and again bled 2 hours after the last dose. The animal was found dead the next day. None of the serums were found to exert any pneumococcidal action when allowed to act for 24 hours at 37 C. in the dark on 1 c c of a culture of pneumococcus Type 1 in dilutions ranging from 1:100 to 1:10,000.

Two other rabbits receiving quinin chlorohydrosulphate behaved in a similar way.

Exper. 5.—Repeated intravenous injections of quinin chlorohydrosulphate, quinin and urea hydrochlorid and quinin dihydrobromid. Three rabbits weighing 1,700, 1,500 and 1,200 gm. were given quinin chlorohydrosulphate, quinin and urea hydrochlorid and quinin dihydrobromid, respectively, in initial doses of 0.01 gm. per kilo. Thirty minutes later bleedings were made. Three hours later a second dose of 0.01 gm. per kilo was given to each and bleedings were made 2 hours after the injections. The serum was at no time pneumococcidal.

The experiments indicate clearly that a single large tolerated dose, a fatal dose, or repeated tolerated doses of varying cinchona derivatives administered either by intravenous or oral route do not serve to render pneumococcidal the serum of rabbits. These results are in accord with those of Wright, Scott and Boecker.

In explanation Scott demonstrated that the destructive power of the rabbit liver for quinin alkaloids is 10 times greater than that of the guinea-pig or mouse. Grosser[9] showed the same holds true for the liver of the cat. Lippmann[10] observed that ethylhydrocuprein exerts its pneumococcidal action in vivo only in the presence of leukocytes. Boecker cites the work of Morgenroth and Ginsberg and suggests that the red blood cells have a special affinity for optochin. This suggestion we find borne out in the quantitative chemical studies of Baldoni[11] who finds that after the administration of quinin to animals by subcutaneous or oral routes, more quinin is demonstrable in the erythrocytes than in the serum. We have elsewhere[12] called attention to the extreme hemolytic power of isotonic solutions of various quinin salts as an index of their affinity for the red blood cells and their property of precipitating serum (and other colloidal solutions) as an index of their lack of affinity for the latter.

SUMMARY

No pneumococcidal action of rabbit serum could be demonstrated after a single large tolerated dose, after a single fatal dose, after repeated injections of tolerated doses either by oral or by intravenous routes of various cinchona derivatives including ethylhydrocuprein hydrochlorid, quinin and urea hydrochlorid, quinin dihydrobromid, and quinin chlorohydrosulphate.

A review of the literature indicates that the liver of the rabbit has a high destructive action on quinin alkaloids and that both leukocytes and red blood cells (but not serum) have a marked affinity for cinchona compounds.

[9] Biochem. Ztschr., 1908, 8, p. 98.

[10] Ztschr. f. Immunitätsforsch., O., 1915, 24, p. 107.

[11] Arch. di Farmacol. sper., 1912, 13, p. 324; abstracted in Zentralbl. f. Biochem. u. Biophysik, 1912-1913, 5, p. 315.

[12] Jour. Infect. Dis., 1918, 22, p. 476.